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CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
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MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU,
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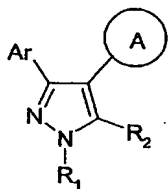
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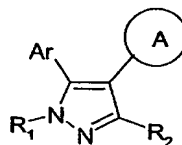
— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PYRAZOLE COMPOUNDS



(IA)



(IB)

(57) Abstract: Compounds of formula (IA) or (IB) or a salt, N-oxide, hydrate or solvate thereof are inhibitors of HSP90, and are of value in the treatment of diseases responsive to HSP90 inhibition such as cancers. In the formulae, Ar is an aryl, aryl(C₁-C₆ alkyl), aryl(C₁-C₆ alkyl), heteroaryl, heteroaryl(C₁-C₆ alkyl), or heteroaryl(C₁-C₆ alkyl) group, any of which being optionally substituted in the aryl or heteroaryl part thereof; R₁ is hydrogen or optionally substituted C₁-C₆ alkyl; R₂ is hydrogen, optionally substituted cycloalkyl, cycloalkenyl, C₁-C₆ alkyl, C₁-C₆ alkenyl, or C₁-C₆ alkynyl; or a carboxyl, carboxamide or carboxyl ester group; and ring A is a non aromatic carbocyclic or heterocyclic ring wherein (i) a ring carbon is optionally substituted, and/or (ii) a ring nitrogen is optionally substituted by a group of formula -(Alk¹)_p (Cyc)_n-(Alk³)_m-(Z)_r (Alk²)_s Q where Alk¹, Alk² and Alk³ are optionally substituted C₁-C₃ alkyl, Cyc is an optionally substituted carbocyclic or heterocyclic radical; m, n, p, r and s are independently 0 or 1, Z is -O-, -S-, -(C=O)-, -SO₂-, -C(=O)O-, -OC(=O)-, -NW-, -C(=O)NRA-, -NRA⁺C(=O)-, -SO₂NRA-, or -NRA⁺SO₂- wherein R^A is hydrogen or C₁-C₆ alkyl, and Q is hydrogen or an optionally substituted carbocyclic or heterocyclic radical.

INTERNATIONAL SEARCH REPORT

Inte Application No

PCT/GB 03/05501

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/38 C07D405/12 C07D401/12 C07D413/12 C07D403/12
C07D417/12 C07D409/12 C07D403/04 C07D405/10 C07D401/04
A61K31/415 //(C07D405/12,307:00,231:00),(C07D401/12,231:00,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	DATABASE CHEMCATS 'Online! AMERICAN CHEMICAL SOCIETY; retrieved from STN XP002275488 RNs 512817-94-6, 512812-41-8, 512817-19-5, 512817-26-4, 494867-78-6 ---	1,2
X,P	WO 03 062206 A (FOSTER RICHARD ;SMITH JULIAN (GB); ARENA PHARMACEUTICALS INC (US);) 31 July 2003 (2003-07-31) examples 87-89,95 ---	1,2,8,23
X	WO 01 79187 A (SHELTON EMMA JANE ;SPENCER JEFFREY R (US); CAI SUI XIONG (US); CYT) 25 October 2001 (2001-10-25) page 74; example 5 --- -/-	1,2,8,23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- *Z* document member of the same patent family

Date of the actual completion of the international search

30 March 2004

Date of mailing of the international search report

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/GB 03/05501

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 213:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 52940 A (ANANTANARAYAN ASHOK ;CRICH JOYCE ZUOWU (US); SELNESS SHAUN RAJ (US) 26 November 1998 (1998-11-26) page 756, line 226 - line 227; claim 69	1,2,8,23
X	WO 97 01551 A (FUJISAWA PHARMACEUTICAL CO ;AKAHANE ATSUSHI (JP); KURODA SATORU (J) 16 January 1997 (1997-01-16) examples 26,44	1,2,8,23
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☒ Further documents are listed in the continuation of box C.

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/GB 03/05501

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMCATS 'Online! AMERICAN CHEMICAL SOCIETY; retrieved from STN XP002275489 RNS 494867-81-1, 442643-27-8, 442642-90-2, 430450-02-5, 442643-55-2, 426252-69-9, 426246-04-7, 428478-82-4, 426242-81-1, 426241-82-9, 428480-97-1, 428479-84-9</p>	1,2
X	<p>PATENT ABSTRACTS OF JAPAN vol. 013, no. 061 (C-567), 10 February 1989 (1989-02-10) - & JP 63 253068 A (NIPPON NOHYAKU CO LTD), 20 October 1988 (1988-10-20) page 45, compound 84</p>	1,2,8,23
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X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BARALDI, P. G. ET AL: "Synthesis and cardiodepressant activity of dialkyl 1,4-dihydro-2,6-dimethyl-4-(pentatomic-het eroaryl)-3,5- pyridinedicarboxylates. 2" retrieved from STN Database accession no. 120:289435 XP002275491 abstract; RN 154926-86-0 & DRUG DESIGN AND DISCOVERY (1993), 10(4), 319-29,</p>	1,2,8,23

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INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/GB 03/05501

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHANKER, M. S. S. ET AL: "A novel synthesis of pyrazolylchromone derivatives" retrieved from STN Database accession no. 116:128767 XP002275492 RN 139394-43-7 & ASIAN JOURNAL OF CHEMISTRY (1992), 4(1), 166-70,</p>	1,2,8
X	<p>----- DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CEKAVICIUS, B. ET AL: "Synthesis and hepatoprotective properties of 4-pyrazolyl-1,4- dihydropyridines" retrieved from STN Database accession no. 108:68683 XP002275493 abstract; RN 112758-37-9 & KHIMIKO-FARMATSEVTICHESKII ZHURNAL (1987), 21(8), 959-65,</p>	1,2,8,23
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/05501

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ALONSO, G. ET AL: "Synthesis of pyrazole C-nucleosides by 1,3-dipolar cycloaddition" retrieved from STN Database accession no. 87:184819 XP002275495 RN 64559-22-4 & ANALES DE QUIMICA (1968-1979) (1976), 72(11-12), 987-90,</p>	1,2,8
X	<p>--- DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ARAKAWA, KIICHI ET AL: "Synthesis of 1-(3-phenylpyrazol-4-yl).beta.-D-ribofuran oside, a C-nucleoside" retrieved from STN Database accession no. 82:73382 XP002275496 RNs 54680-27-2, 54680-28-3, 54680-29-4, 54680-30-7 & CHEMISTRY LETTERS (1974), (11), 1305-8,</p>	1,2,8
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INTERNATIONAL SEARCH REPORT

Int lional Application No

PCT/GB 03/05501

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BORRACHERO-MOYA, PASTORA ET AL: "Synthesis of 4-(4,6-di-O-benzyl-2,3-dideoxy-.beta.-D-er ythro-hex-2- enopyranosyl)pyrazoles from 3,4,6-tri-O-acetyl-D-glucal" retrieved from STN Database accession no. 129:189545 XP002275499 RNs 211674-08-7, 211674-06-5, 211674-15-6 & CARBOHYDRATE RESEARCH (1998), 308(1-2), 181-190,</p>	1,2,8
X	<p>----- DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BARALDI, P. G. ET AL: "Synthesis and cardiodepressant activity of dialkyl 1,4-dihydro-2,6-dimethyl-4-(pentatomic-het eroaryl)-3,5- pyridinedicarboxylates. 2" retrieved from STN Database accession no. 120:289435 XP002275500 RN 154926-87-1 & DRUG DESIGN AND DISCOVERY (1993), 10(4), 319-29,</p>	1,2,8,23
X	<p>----- DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GHOSH, CHANDRA KANTA ET AL: "Benzopyrans. 31. Reaction of 1,1-diacetyl-2-(6-methyl-4-oxo-4H-1- benzopyran-3-yl)ethylene with phenyldiazomethane" retrieved from STN Database accession no. 119:270955 XP002275501 RN 151466-29-4 & TETRAHEDRON (1993), 49(19), 4135-40,</p> <p>----- -/--</p>	1,2,8

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/GB 03/05501

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MORENO-MANAS, MARCIAL ET AL: "Hindered rotation around C(sp²)-C(sp³) bonds in the enol forms of .alpha.-(9-fluorenyl)-.beta.-diketones and in 3,5-disubstituted 4-(9-fluorenyl)pyrazoles. A proton NMR study" retrieved from STN Database accession no. 110:74500 XP002275502 RN 118365-08-5 & BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN (1988), 61(5), 1827-9,</p>	1,2,8
X	<p>----- DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GONZALEZ, A. ET AL: "Metal complexes in organic synthesis. Preparation of .alpha.-(1-adamantyl)-.beta.-dicarbonyl compounds and 4-(1-adamantyl)-3,5-disubstituted pyrazoles and -isoxazoles" retrieved from STN Database accession no. 106:213817 XP002275503 RN 108221-13-2 & TETRAHEDRON (1986), 42(15), 4253-7,</p>	1,2,8
X	<p>----- DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BOBOWSKI, GEORGE ET AL: "4-Substituted-3-alkyl-3,4-dihydro-2H-1,3- benzoxazin-2-ones. IV. Keto-enol tautomerism of .beta.-keto ester derivatives. Reaction of .beta.-dicarbonyl compounds with diamines" retrieved from STN Database accession no. 93:168205 XP002275504 RN 74834-76-4 & JOURNAL OF HETEROCYCLIC CHEMISTRY (1980), 17(3), 519-28,</p>	1,2,8
A	<p>----- WO 00 31063 A (CRICH JOYCE Z;ANANTANARAYAN ASHOK ; CLARE MICHAEL (US); SEARLE & C) 2 June 2000 (2000-06-02) abstract; claims 1,3,135,139,140 ----- -/--</p>	1-21, 23-25

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/05501

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BANNIER A ET AL: "DETERMINATION OF A NEW ANTI-INFLAMMATORY AGENT, 1-ISOBUTYL-3,4-DIPHENYLPYRAZOLE-5-ACETIC ACID, BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY"</p> <p>JOURNAL OF PHYSIOLOGY, XX, XX, vol. 227, no. 1, 8 January 1982 (1982-01-08), pages 213-218, XP009008354</p> <p>ISSN: 0022-3751</p> <p>the whole document</p>	1-21, 23-25
A,P	<p>WO 03 055860 A (CANCER RES TECHNOLOGY LTD ;DRYSDALE MARTIN JAMES (GB); PEARL LAURE)</p> <p>10 July 2003 (2003-07-10)</p> <p>the whole document</p>	1-21, 23-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/05501

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 22, 26 and 27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The presently claimed subject-matter relates to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds as illustrated by the examples wherein Ar represents always a (optionally substituted) phenyl group directly linked to the pyrazole core.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 03/05501

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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